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REVIEW

Endoscopic Ultrasonography In Portal Hypertension

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ABSTRACT

Endoscopic ultrasonography (EUS) has recently emerged as an alternative means of providing data for patients with portal hypertension that is more accurate, less invasive and reproducible. It is well established that video-echo endoscopy, with combined endoscopic and sonographic examination, is comparable to endoscopy in diagnosing esophageal varices, but is more sensitive in diagnosing the presence of gastric varices. Dilated venous abnormalities outside the gastroesophageal lumen, which cannot be diagnosed by endoscopy, are readily visible by means of EUS or miniature probes. In the clinical setting of portal hypertension, endoscopic ultrasonography is also useful to predict the risk of variceal recurrence or rebleeding, which cannot be reliably predicted using endoscopy alone. The introduction of echo endoscopes equipped with Doppler facilities together with the performance of haemodynamic studies has allowed sonographic visualization of the vessels, playing thus an important role in the management of cirrhotic patients. It has thus become feasible not only to assess the vascular blood flow but also to evaluate possible morphologic and haemodynamic changes of the vessels after endoscopic or pharmacologic therapy. It is, nowadays, obvious that EUS is an exciting technological advance that has established its position in the diagnosis of varices and cirrhosis; what lies ahead for EUS is to positively find application in predicting the risk of variceal bleeding and in managing portal hypertension.

ABBREVIATIONS:
EUS = Endoscopic Ultrasonography
EGD = Esophagogastroduodenoscopy
ECV = Esophageal Collateral Veins
GCV = Gastric Collateral Veins

KEY WORDS: *EUS, portal hypertension, gastroesophageal varices, variceal recurrence, rebleeding, venous blood flow*

INTRODUCTION

Over the past two decades, endoscopic ultrasonography (EUS) has undergone a transition from being a novel imaging technique to becoming a clinical diagnostic test that is necessary for the optimal management of gastrointestinal diseases. Along with established clinical indications, such as gastrointestinal and pancreatic tumor staging, differential diagnosis of submucosal lesions, evaluation of solid and cystic pancreatic masses, detection of lymph nodes and fine needle aspiration (FNA), new applications have been suggested. Of great interest has been the effort of endosonographers to define a clinical role for EUS in portal hypertension.

Since its first use in the assessment of patients with portal hypertension in the mid-1980s [1], many conflicting studies have been published. Nowadays, EUS has an established role in diagnosing varices and portal hypertension, and assessing the risk of recurrent varices and variceal hemorrhage as well as in evaluating the success of pharmacologic, endoscopic and shunt therapy for portal hypertension.

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EUS FOR THE DIAGNOSIS OF VARICES AND PORTAL HYPERTENSION

The venous anatomy of the lower esophagus is composed of four layers: intraepithelial channels, superficial venous plexus, deep submucosal veins and adventitial veins radiating from the inner esophageal mucosa to the outer layer [2]. The innermost venous plexus communicates with the extrinsic plexus via perforating veins [3], which are commonly present 1-5 cm above the gastroesophageal junction. These, in turn, drain into the tributaries of either the portal or the azygos veins. Development of portal hypertension causes diversion of blood from the drainage bed of the portal vein to that of the azygos system, causing engorgement of all the previous channels. Thus, the dilated deep submucosal veins are seen as variceal columns and the dilated adventitial veins form paraesophageal varices.

Currently, the most widely accepted modality for screening gastroesophageal varices is esophagogastroduodenoscopy (EGD), which, however, may be subjected to high interobserver variation in the assessment of variceal size [4-5], lacks sensitivity in the diagnosis of gastric varices [6,7] and, finally, cannot assess the variceal wall thickness. The results of the older large-bore fiberoptic echo endoscope and the use of the balloon-insufflation technique, which caused esophageal wall compression resulting in lower sensitivity of EUS in detecting esophageal varices, were disappointing [7,8]. EUS was able to demonstrate only 14-25% of grade I, 73-78% of grade II and 50-89% of grade III of endoscopically confirmed esophageal varices [7,8]. With advances in technology, the new generation video-echo endoscope has a significantly reduced scope diameter, and an improvement in ease of scope manipulation and endoscopic image. Thus, by directly visualizing the esophageal lumen rather than relying only on sonographic examination, the diagnosis of esophageal varices has been enhanced. As shown in a recent study [6], EUS seems to be as good as EGD for the screening of esophageal varices with a sensitivity, specificity, PPV and NPV rate of 96.4%, 95.8%, 96.4% and 95.8%, respectively (Table 1). Moreover, in the same study, the superiority of EUS in detecting gastric varices in comparison to EGD was once more demonstrated [8-10]. Using EUS as the gold standard, the sensitivity, specificity, PPV and NPV rates of EGD in the diagnosis of gastric varices were 43.8%, 94.4%, 77.8% and 79.1%, respectively (Table 1). Finally, the use of high-frequency (20 MHz) miniature US probes can also increase the sensitivity of detecting gastroesophageal varices [11].

Apart from the gastroesophageal varices, portal hypertension causes engorgement and increased blood flow in the collaterals vessels surrounding the lower esophagus and proximal stomach outside the esophageal wall. The collateral veins are divided in peri-esophageal (peri-ECV), located adjacent to the muscularis externa of the esophagus and para-esophageal (para-ECV), external to the esophageal wall, and in no contact with the muscularis externa. Similarly, collateral veins surrounding the proximal stomach are divided in peri-gastric (peri-GCV) and para-gastric collateral veins (para-GCV). Veins connecting peri-ECVs with para-ECVs are called connecting veins, whereas those, connecting esophageal varices with peri-ECVs, are the perforating veins. Although these vessels have been examined by percutaneous transhepatic portography [2], the latter is an invasive method which, in addition, is unable to differentiate the submucosal varices from peri-ECVs. Similarly, routine CT is highly costly and not very sensitive in detecting paraesophageal varices [12-13]. With the availability of better instrumentation, both the anatomy and physiology of the venous circulation of the esophagus and stomach can be characterized with relative clarity by endoscopic ultrasonography [6,14-16]. Based on the venous abnormalities, it was found that the sensitivity, specificity, PPV and NPV rates of EUS in the diagnosis of portal hypertension were 92.3%, 94.6%, 84.2% and 97.5%, respectively, whereas the sensitivity, specificity, PPV and NPV rates of EGD alone were 57.7%, 100%, 100% and 88.3% (Table 2), as EGD does not detect the extraluminal vascular changes that occur in patients with portal hypertension [6]. These results were echoed in another study, where the presence of peri-ECVs was 97% sensitive and 97% specific for cirrhosis, a diagnostic yield significantly better than endoscopy, which identified esophageal varices in only 74% of patients with cirrhosis [16]. Moreover, it was shown that the higher the variceal size at endoscopy, the more readily visualized were the peri-ECVs at EUS, in contrast to the para-ECVs, where no significant correlation was observed [15]. This is in contrast to a more recent study,

TABLE 1. EUS and EGD in diagnosing esophageal (EV) and gastric (GV) varices respectively

	Sensitivity	Specificity	PPV	NPV
EUS in diagnosing EV	96.4%	95.8%	96.4%	95.8%
EGD in diagnosing GV	43.8%	94.4%	77.8%	79.1%

EGD = Esophagogastroduodenoscopy, EUS = Endoscopic Ultrasonography, EV = Esophageal varices, GV = Gastric varices

TABLE 2. EUS and EGD in diagnosing portal hypertension

	Sensitivity	Specificity	PPV	NPV
EUS	92.3%	94.6%	84.2%	97.5%
EGD	57.7%	100%	100%	88.3%

EUS = Endoscopic Ultrasonography, EGD = Esophagogastroduodenoscopy, PPV = Positive Predictive Value, NPV = Negative Predictive Value

which showed that both para-ECVs and peri-ECVs were associated with larger esophageal varices [6]. This discrepancy was attributed to the largest sample size and to the use of the echo endoscope rather than the miniature ultrasound probe, which may underestimate the prevalence and degree of para-ECVs due to the limited penetration depth. The latter study additionally demonstrated a positive correlation between the size of peri-ECV and para-ECV with the Child-Pugh grading of cirrhosis and between the grade of gastric varices with the size of para-GCV and peri-GCV and confirmed previous data about the strong association between the perforating veins and the size of esophageal and gastric varices.

Another difference between cirrhotic and noncirrhotic patients recognized by EUS, was the thickness of gastric mucosa and submucosa, which was found to be greater in cirrhotic patients, reflecting the relative outflow obstruction of venous and lymphatic flow in these patients [16].

The dilation of the azygos vein is an issue that has provoked many controversies. Although it has been reported that portal hypertension causes dilation of splenic vein, portal vein and superior mesenteric vein when comparing EUS findings in cirrhotic and noncirrhotic patients, it has no significant influence on the diameter of the azygos vein [8]. This was validated subsequently, where patients with more severe liver disease did not have significantly larger azygos vein diameters [17]. On the contrary, other studies showed a significant dilation of the azygos vein in cirrhosis [7,16,18], as it constitutes the main drainage pathway for the superior portosystemic collateral circulation.

Another sign of portal hypertension, identifiable by EUS seems to be the dilation of the thoracic duct [8,16,19]. The hepatic venous outflow obstruction and increased hepatic lymph formation cause distention of the hilar lymphatics, resulting in increase of lymph flow through the thoracic duct. Even though the dilation of the thoracic duct was found only in patients with ascites and varices [19], a larger sample size must be evaluated in order to identify differences between subgroups of cirrhotic patients. Nonetheless, EUS may be useful for studying the thoracic duct in determining its potential role in ascites formation.

EUS can also be used for the detection of rectal varices. As it was shown [20], prevalence of rectal varices was 43.3% on endoscopy and 75% on EUS whereas congestive rectopathy was found in 38.3% of patients. These vascular changes seemed to be influenced by sclerotherapy, but not by the grade of esophageal varices, Endosonography has been used in the evaluation of cirrhotic patients. by the cause of portal hypertension, or by the severity of liver disease.

It is of great importance, that the new generation linear echo endoscopes can evaluate the vascular blood flow, by using Duplex or Doppler sonography (CD-EUS). Thus, diminished or reversed direction of vascular blood flow or even the patency of a vessel or a shunt can be recognized. Other methods used to measure the azygos blood flow are the invasive thermodilution technique [21] and the MR angiography [22], which, although non-invasive, does not allow continuous haemodynamic measurement. The haemodynamic study of the azygos vein can be easily done by CD-EUS, finding a straight segment of the vein. The character of azygos blood flow (AzBF) appears as a smooth venous tracing in the spectral display with small fluctuations associated with the patient's breathing [17,18]. Maximal blood flow velocity seems to be increased in patients with portal hypertension and gastroesophageal varices [18], indicating that AzBF is related to the severity of liver disease as reflected in Child-Pugh grading [17]. The morphology and the blood flow through the left gastric vein has been studied with CD-EUS [23] and it was shown that, although its diameter increased as the size of the varices increased, this increase was not statistically significant. It was suggested that the increased hepatofugal flow velocity was the most sensitive marker for the development of varices. Furthermore, the branching pattern of the left gastric vein, as it has been described with left gastric venography [24,25], and its relationship with topographic collateral channels, may be responsible for directing the blood flow towards varices at the level of the proximal stomach. Finally, Duplex endosonography can be used to identify the patency of intra-abdominal vessels, such as splenic and portal vein, or of a portosystemic shunt when transabdominal ultrasound is nondiagnostic in patients with suspected thrombosis [26].

EUS IN THE ASSESSMENT OF VARICEAL RECURRENCE AND REBLEEDING

The hepatofugal blood flow velocity in the left gastric vein trunk, and its branching pattern, were associated with variceal recurrence after endoscopic therapy [23]. After endoscopic variceal ligation or sclerotherapy, the increased hepatofugal velocity and the anterior branching pattern, documented by CD-EUS, were found to be risk factors for recurrence [27]. The detection rate and diameter of the perforating veins may also be a predictor of variceal reccurence [23].

Endosonographically detected paraesophageal varices are excellent indicators of variceal recurrence after endoscopic sclerotherapy or ligation [28-30]. Patients with large (>5 mm) para-ECVs have a greater risk of variceal recurrence (93%) and bleeding (43%) than those with small or without para-ECVs (46% and 12% respectively) [29] (Table 3). These findings were confirmed by subsequent studies [16,30]. It was also suggested that the presence of large para-gastric collateral veins (maximal diameter >5 mm) may be an additional risk factor for a first variceal hemorrhage [16].

Severe type peri-ECVs and large perforating veins were detected endosonographically, three months before endoscopic variceal recurrence [31], indicating that these vessels may be

TABLE 3. Risk of variceal recurrence and rebleeding according to para-ECVs' size

Size of para-ECVs	Variceal recurrence	Variceal rebleeding
>5 mm	93%	43%
<5 mm	46%	12%

ECV = Esophageal Collateral Veins

used as well, for the early prediction of variceal recurrence after endoscopic treatment. Additionally, the presence of multiple intramural vessels in the cardia may predict recurrence [31,32].

Furthermore, in assessing the risk of variceal bleeding, EUS is very useful, as it allows the evaluation of the variceal size and variceal wall thickness [33], the measurement of intravariceal pressure by direct puncture of the varices [34], by using a pressure sensitive gauge [35] or by Doppler-guided manometry [36] and the detection of high-risk stigmata of varices such as the red hematocystic spot, which can be identified by miniprobes [37].

EUS AND ENDOSCOPIC THERAPY OF VARICES

It is well known that varices recur more commonly among patients who undergo endoscopic variceal ligation compared to those who had sclerotherapy [38,39], as ligation provokes mechanical strangulation of the varices in the mucosal and submucosal layers, leaving the perforating veins, which join the submucosal vascular channels to para-esophageal collateral veins, untouched. On the other hand, sclerotherapy may be able to obliterate the perforating veins and feeding veins, while chemical irritation caused by the sclerosants induce fibrosis and thickening of the inner esophageal wall, preventing variceal recurrence.

By using miniprobes, perforating veins can be identified and bands can be applied on them, increasing thus the success of ligation [40] and the variceal recurrence-free interval [41]. Moreover, by using CD-EUS, the sclerosant can be injected until the varix is seen to be completely thrombosed, as indicated by the absence of flow on Doppler, or it can be directed to the level of the perforating veins [42]. Thus, the number of sessions required for obliteration of esophageal varices and the recurrence rate may be decreased. Additionally, EUS can be of value in detecting residual varices, which are less apparent in endoscopy after several sessions of sclerotherapy, because of overlying ulceration, edema and formation of pseudopolyps. The same stands for the gastric varices, which cannot be easily detected endoscopically, mostly after cyanoacrylate injection for controlling gastric variceal bleeding [43]. EUS can easily identify residual gastric varices as submucosal anechoic vascular channels with a color Doppler signal. Persistence of blood flow, as detected by CD-EUS, is associated with a higher failure rate of variceal obliteration by endoscopic treatment and with a higher risk of gastric variceal recurrent bleeding compared to those without detectable blood flow [43]. It is also noteworthy, that patients who underwent repeated EUS-guided cyanoacrylate injection had a significantly lower risk of rebleeding. Even though the overall mortality rate was not significantly changed, it was significantly improved, in comparison to the equivalent mortality rate of patients who received on-demand injection only at the time of recurrent bleeding [43].

EUS FOR THE EVALUATION OF THE EFFECTS OF PHARMACOLOGIC THERAPY

As it has been previously mentioned, by using CD-EUS, the AzBF was found to have a positive association with the severity of liver disease as reflected in Child-Pugh grading [17]. A marked reduction in AzBF was documented after intravenous injections of terlipressin or somatostatin, being, in the case of somatostatin, more dramatic in the first minute after bolus injection [17]. These findings were confirmed in another study [44], where continuous infusion of somatostatin or octreotide was applied so as to assess the effects of these drugs in AzBF and in gastric mucosal blood flow. An immediate and transient decrease in AzBF and gastric mucosal blood flow was demonstrated during continuous infusion of either drug. Somatostatin induced a significant rebound effect 60 minutes after administration, suggesting a possible desensitization phenomenon.

Patients on propranolol or isosorbide-5-mononitrate were examined by serial EUS and endoscopic gauge measurement to determine the effect of these drugs on variceal volume and pressure [35]. It was shown that whereas isosorbide-5-mononitrate reduced only transmural variceal pressure, in the case of propranolol, the overall reduction in the variceal wall tension exceeded that contributed by transmural pressure change, showing that propranolol reduced not only the variceal pressure, but also the variceal column radius and volume.

CONCLUSIONS

The current status of non-invasive methods for the assessment of portal haemodynamics and risk of variceal bleeding is still unsatisfactory and can not be recommended for routine clinical use. HVPG is the best predictor of the efficacy of pharmaceutical therapy and along with the endoscopic appearance of varices provide valuable information regarding risk

stratification and management of high-risk patients. However, EUS appears promising but requires further evaluation.

EUS can provide significant information regarding the morphologic assessment of varices. It is not clear however, if variceal wall thickness alone is as accurate a predictor of bleeding or whether simultaneous intravariceal pressure measurements should be added in a prognostic model that could allow risk stratification based on pathophysiological implications. Moreover, it is clear that it can be used for risk stratification after endoscopic therapy, but it is not known if this approach would be beneficial in clinical practice. Perhaps a more strict endoscopic screening should be applied in patients with large para-oesophageal collateral veins after endotherapy in order to prevent further bleeding episodes, and this could be a rather interesting area for future research.

In conclusion, EUS is a valuable imaging method for investigating patients with portal hypertension. Although its role in the evaluation of bleeding risk and response to therapy is still not well defined, the fact is that EUS provides an accurate diagnosis, identifies high-risk patients, and allows the assessment of success of endoscopic and pharmacologic therapies.

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